(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 1999 (29.12.1999)

PCT

(10) International Publication Number
WO 99/66951 A3

(51) International Patent Classification[6]: A61K 51/08, 47/48, C07K 16/46, C12N 15/62, 15/13 // 5/10, 1/21

(21) International Application Number: PCT/US99/13879

(22) International Filing Date: 22 June 1999 (22.06.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/090,142	22 June 1998 (22.06.1998)	US
60/104,156	14 October 1998 (14.10.1998)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/090,142 (CIP)
Filed on	22 June 1998 (22.06.1998)
US	60/104,156 (CIP)
Filed on	14 October 1998 (14.10.1998)

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

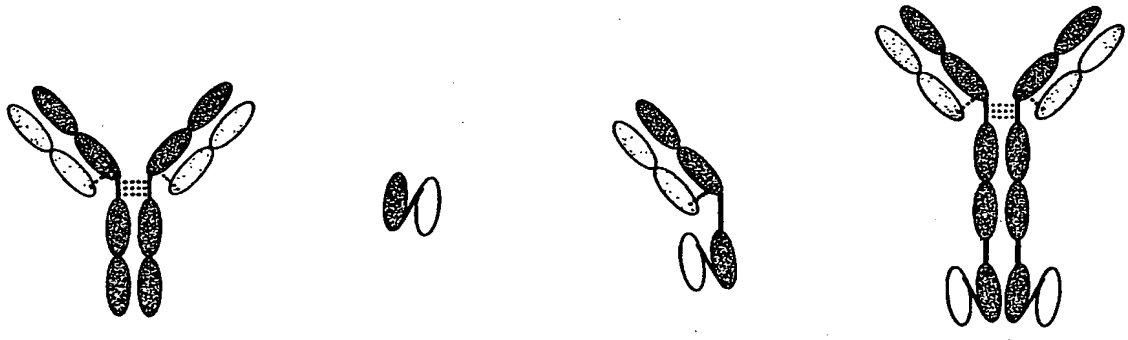
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
15 June 2000

[Continued on next page]

(54) Title: USE OF BI-SPECIFIC ANTIBODIES FOR PRE-TARGETING DIAGNOSIS AND THERAPY



(57) Abstract: The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate. The targetable conjugate comprises a carrier portion which comprises or bears at least one epitope recognizable by at least one arm of said bi-specific antibody or antibody fragment. The targetable conjugate further comprises one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bi-specific antibodies or antibody fragments, as well as methods for using them.

WO 99/66951 A3

Date of publication of the revised international search report: 1 February 2001

(15) Information about Correction:
see PCT Gazette No. 05/2001 of 1 February 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

REVISED VERSION

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 99/13879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K51/08 A61K47/48 C07K16/46 C12N15/62 C12N15/13
//C12N5/10,C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KARACAY, H. ET AL: "Studies on a humanized anti-CEA x murine anti-(In- DTPA) bispecific antibody construct for radioimmunotherapy of CEA-positive tumors." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, (MARCH, 1999) VOL. 40, PP. 644. MEETING INFO.: 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH PHILADELPHIA, PENNSYLVANIA, USA APRIL 10-14, 1999 AMERICAN, XP002120429 abstract --- -/--	1,3, 9-17, 19-30, 32-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2000	03.07.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KARACAY, H. (1) ET AL: "Pretargeting studies with a humanized anti-CEA X murine anti-(In- DTPA) bispecific antibody construct and Tc-99m/Re-188 labeled peptide." JOURNAL OF NUCLEAR MEDICINE, (MAY, 1999) VOL. 40, NO. 5 SUPPL., PP. 225P. MEETING INFO.: 46TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE LOS ANGELES, CALIFORNIA, USA JUNE 6-10, 1999 SOCIETY OF NUCLEAR MEDICINE., XP002120430 abstract	1,3, 9-17, 19-30, 32-34
X	GAUTHEROT E ET AL: "Delivery of therapeutic doses of radioiodine using bispecific antibody -targeted bivalent haptens." JOURNAL OF NUCLEAR MEDICINE, (1998 NOV) 39 (11) 1937-43., XP002120432 see discussion page 1937, column 2, paragraphs 4,5	1,3, 9-17, 19-30, 32-34
X	BODERE, F. KRAEBER (1) ET AL: "Phase I/II total of two-step radioimmunotherapy in medullary thyroid cancer (MTC) using bispecific anti-CEA/anti- DTPA -in antibody and iodine-131-labeled bivalent hapten." JOURNAL OF NUCLEAR MEDICINE, (MAY, 1998) VOL. 39, NO. 5 SUPPL., PP. 246P. MEETING INFO.: 45TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE TORONTO, ONTARIO, CANADA JUNE 7-11, 1998 SOCIETY OF NUCLEAR MEDICINE., XP002120769 abstract	1,3, 9-17, 19-30, 32-34
X	BARDIES M. ET AL: "Bispecific antibody and iodine-131-labeled bivalent hapten dosimetry in patients with medullary thyroid or small-cell lung cancer" JOURNAL OF NUCLEAR MEDICINE, vol. 37, November 1996 (1996-11), pages 1853-1859, XP002116384 see discussion abstract page 1853, column 2, paragraph 4	1,3, 9-17, 19-30, 32-34
X	KRAEBER-BODERE F ET AL: "Bispecific antibody and bivalent hapten radioimmunotherapy in CEA-producing medullary thyroid cancer xenograft." JOURNAL OF NUCLEAR MEDICINE, (1999 JAN) 40 (1) 198-204., XP002120433 see discussion page 199, column 1	1,3, 9-17, 19-30, 32-34

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOSONO M ET AL: "Biodistribution and dosimetric study in medullary thyroid cancer xenograft using bispecific antibody and iodine-125-labeled bivalent hapten." JOURNAL OF NUCLEAR MEDICINE, (1998 SEP) 39 (9) 1608-13., XP002120434 abstract see discussion page 1608, column 2, paragraph 3 ---	1,3, 9-17, 19-30, 32-34
X	KRANENBORG M H ET AL: "Development and characterization of anti-renal cell carcinoma x antichelate bispecific monoclonal antibodies for two-phase targeting of renal cell carcinoma." CANCER RESEARCH, (1995 DEC 1) 55 (23 SUPPL) 5864S-5867S., XP002120435 see discussion abstract ---	1,3, 9-17, 19-30, 32-34
Y	KRANENBORG M H ET AL: "Two-step radio-immunotargeting of renal-cell carcinoma xenografts in nude mice with anti-renal-cell-carcinoma X anti- DTPA bispecific monoclonal antibodies." INTERNATIONAL JOURNAL OF CANCER, (1998 JAN 5) 75 (1) 74-80., XP002120436 see discussion abstract ---	1,3, 9-17, 19-30, 32-34
X	GAUTHEROT E ET AL: "Therapy for colon carcinoma xenografts with bispecific antibody -targeted, iodine-131-labeled bivalent hapten" CANCER, vol. 80, no. SUPPL. 12, 15 December 1997 (1997-12-15), pages 2618-2623, XP002110873 see discussion abstract ---	1,3, 9-17, 19-30, 32-34
X	WO 96 04313 A (IMMUNOMEDICS INC) 15 February 1996 (1996-02-15) page 7, line 13-17 page 37, line 14-17; example 4 ---	1,3,7, 9-17, 19-30, 32-34
X	BOSSLET K. ET AL: "Generation of bispecific monoclonal antibodies for two phase radioimmunotherapy." BRITISH JOURNAL OF CANCER, (1991) 63/5 (681-686)., XP002120437 abstract; example 4 page 683; example 4 ---	1,3, 9-17, 19-30, 32-34

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 623 675 A (HYBRITECH INC) 9 November 1994 (1994-11-09) abstract; example 4 page 8, line 45-50; example 4	1,3,7, 9-17, 19-30, 32-34
X	EP 0 419 387 A (IMMUNOTECH PARTNERS) 27 March 1991 (1991-03-27) page 8, line 45-50; claims 6,15; examples 5,8	1,3,7, 9-17, 19-30, 32-34
X	MANETTI, CORINE ET AL: "Intracellular uptake and catabolism of anti-IgM antibodies and bi - specific antibody -targeted hapten by B-lymphoma cells" INT. J. CANCER (1995), 63(2), 250-6, XP002120770 page 251; claims 6,15; examples 5,8	1,3, 9-17, 19-30, 32-34
X	BARBET, J. ET AL: "Radioimmunotherapy of LS174T colon carcinoma in nude mice using an iodine-131-labeled bivalent hapten combined with an anti-CEAX anti-indium-DTPA bispecific antibody." TUMOR BIOLOGY, (SEPT., 1997) VOL. 18, NO. SUPPL. 2, PP. 31. MEETING INFO.: MEETING ON FROM BASIC CANCER RESEARCH TO CLINICAL APPLICATION HELD AT THE XXVTH ANNIVERSARY MEETING OF THE INTERNATIONAL SOCIETY FOR ONCODEVELOPMENTAL BIOLOGY AND MEDICINE MON, XP002120771 abstract; claims 6,15; examples 5,8	1,3, 9-17, 19-30, 32-34
X	US 5 591 828 A (BOSSLET KLAUS ET AL) 7 January 1997 (1997-01-07) abstract; claims 6,15; example 5	1,3,7, 9-17, 19-30, 32-34
Y	MCGUINNESS B. T. ET AL: "Phage diabody repertoires for selection of large numbers of bispecific antibody fragments" NATURE BIOTECHNOLOGY, vol. 14, September 1996 (1996-09), pages 1149-1154, XP002100039 page 1149; figures 1,2	1,3,7, 9-17, 19-30, 32-34

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	ALT M. ET AL: "Novel tetravalent and bispecific IgG-like antibody molecules combining single chain diabodies with the immunoglobulin gamma-1 or CH3 region" FEBS LETT, vol. 454, 1999, pages 90-94, XP002120438 see discussion abstract; figure 1 ---	1,3,7, 9-17, 19-30, 32-34
Y,P	OLAFSEN T B ET AL: "IgM secretory tailpiece drives multimerisation of bivalent scFv fragments in eukaryotic cells" IMMUNOTECHNOLOGY, vol. 4, no. 2, October 1998 (1998-10), page 141-153 XP004153638 abstract; figure 2 ---	1,3,7, 9-17, 19-30, 32-34
X	EP 0 263 046 A (IMMUNOTECH SA) 6 April 1988 (1988-04-06) abstract ---	1,3,7, 9-17, 19-30, 32-34
X	EP 0 511 011 A (SURFACE ACTIVE LTD) 28 October 1992 (1992-10-28) abstract ---	1,3,7, 9-17, 19-30, 32-34
X	WO 98 08875 A (BOHLEN HERIBERT ;VIVA DIAGNOSTIKA DIAGNOSTISCHE (DE)) 5 March 1998 (1998-03-05) page 13 -page 14; claim 40; figure 1; examples 7,10 ---	1,3,7, 9-17, 19-30, 32-34
X,P	KIPRIYANOV S. M. ET AL: "Bispecific tandem diabody for tumor therapy with improved antigen binding and pharmacokinetics" J MOL. BIOL., vol. 293, no. 1, October 1999 (1999-10), pages 41-56, XP002131382 abstract; figures 1,9,10 -----	1,3,7, 9-17, 19-30, 32-34

INTERNATIONAL SEARCH REPORT

Inter. onal application No.
PCT/US 99/13879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1, 3, 12-17, 19-30, 32-34
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

3,7,9-11 complete, 1, 12-17, 19-30, 32-34 partially

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-29 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claims 1-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1, 3, 12-17, 19-30, 32-34

Present claims 1, 3, 12-17, 19-30, 32-34 relate to a method and the corresponding kit defined by reference (inter alia) to the following parameters: a clearing composition, a first targetable conjugate, conjugated therapeutic or diagnostic agents or enzymes, a prodrug, a drug, etcetera.
The claims cover all products having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).
Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products and methods mentioned in the description in examples and those specified in the claims and to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 3 complete, 1, 12-17, 19-30, 32-34 partially

   Method of treating diseased tissues in a patient comprising:
   A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
   B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
   C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated radioactive isotope as therapeutic agent.
   Pharmaceutical kits for performing the method.

2. Claims: 4, 5 complete, 1, 12-17, 19-30, 32-34 partially

   Method of treating diseased tissues in a patient comprising:
   A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
   B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
   C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated boron compounds as therapeutic agent.
   Pharmaceutical kits for performing the method.

3. Claims: 6 complete, 1, 12-17, 19-30, 32-34 partially

   Method of treating diseased tissues in a patient comprising:
   A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
   B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
   C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated toxins as therapeutic agent.
   Pharmaceutical kits for performing the method.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

4. Claims: 7 complete, 1, 12-17, 19-30, 32-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated drug as therapeutic agent.
Pharmaceutical kits for performing the method.

5. Claims: 18 complete, 1, 12-17, 19-30, 32-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated hapten as therapeutic agent.
Pharmaceutical kits for performing the method.

6. Claims: 9,11 complete, 1, 12-17, 19-30, 32-34 partially

Method of identifying diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated radioactive isotopes as diagnostic agent.
Pharmaceutical kits for performing the method.

7. Claims: 10 complete, 1, 12-17, 19-30, 32-34 partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method of identifying diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated MRI imaging agents as diagnostic agent.
Pharmaceutical kits for performing the method.

8. Claims: 1, 12-17, 19-30, 32-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated enzymes
D) further administering a prodrug where said enzyme is capable of converting said prodrug to a drug at the target site.
Pharmaceutical kits for performing the method.

9. Claims: 1, 12-17, 19-30, 32-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated enzymes
D) further administering a drug which is capable of beeing detoxified to form an intermediate of lower toxicity and said enzyme is capable of reconverting the detoxified intermediate to a toxic form and therefore increasing

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

toxicity of said drug at the target site.
Pharmaceutical kits for performing the method.

10. Claims: 1,2,8 12-17, 19-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated enzymes
D) further administering a prodrug which is activated through natural processes and subject to detoxification (conversion to a lower toxicity intermediate), where said enzyme is capable of reconverting said detoxified intermediate to a toxic form and therefore increasing toxicity of said drug at the target site.
Pharmaceutical kits for performing the method.

11. Claims: 1,2,8 12-17, 19-34 partially

Method of treating diseased tissues in a patient comprising:
A) administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate
B) optionally administering a clearing composition and allowing to clear non-localized antibodies or antibody fragments from circulation.
C) administering a first targetable conjugate comprising a carrier portion that bears epitope recognizable by said one other arm of bi-specific antibody or antibody fragment and one or more conjugated enzymes
D) further administering a second targetable conjugate which comprises a carrier portion that bears epitope recognizable by at least one other arm of bi-specific antibody or antibody fragment and a prodrug where said enzyme is capable of converting said prodrug to a drug at the target site.
Pharmaceutical kits for performing the method.

12. Claims: 35-50

A recombinant DNA construct comprising an expression cassette or a set of expression cassettes capable of producing in a host cell a bi-specific antibody or antibody fragment or bispecific fusion protein having at least one

arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate. A method of preparing a bi-specific antibody or antibody fragment or bispecific fusion protein having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati... Application No
PCT/US 99/13879

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9604313 A	15-02-1996	US	5686578 A	11-11-1997
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